Please add the following new claims:

26. The viral vector of claim 19, wherein the vascular endothelial growth factor is $VEGF_{121}$ or $VEGF_{165}$.

C6 SubD3

27. The bone graft of claim 22, wherein the vascular endothelial growth factor is $VEGF_{121}$ or $VEGF_{165}$.

## Remarks

### Summary of Invention

The invention is drawn to a method of enhancing bone density or formation (claims 1-12 and 17-18), a viral vector (claims 19-21 and 26), and a bone graft (claims 22-23, 25, and 27).

### Discussion of Office Action

The Office Action rejects claims 1-3, 6-12, 17-23, and 25 as allegedly not enabled. The Office Action also rejects claims 19-21 as obvious in light of Bonadio et al. (U.S. Patent 5,942,496) (hereinafter "Bonadio"). Claims 4, 5, 13-16, and 24 are objected to as being dependent upon a rejected base claim. The Office Action indicates that claims 4, 5, 13-16, and 24 would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

### Discussion of Amendment to the Specification

The specification at page 3, line 2 has been amended to correct an obvious typographical error. In particular, "$FEGF_D$" has been changed to "$VEGF_D$". This amendment adds no new matter to the application.

### Discussion of Claim Amendments

Claims 1 and 19 are amended to more particularly point out and distinctly claim the present invention by specifying that the first nucleic acid encodes a vascular endothelial growth factor. Similarly, claim 22 is amended to more particularly point out and distinctly claim the present invention by specifying the first exogenous nucleic acid encodes a vascular endothelial growth factor. Claim 4 is amended to more particularly point out and distinctly claim the present invention by specifying that the vascular endothelial growth factor is $VEGF_{121}$ or $VEGF_{165}$. Claim 5 is amended to more particularly point out and distinctly claim the present invention by specifying that the vascular endothelial growth factor is selected from the group consisting of $VEGFA_{138}$, $VEGFA_{162}$, $VEGF_{182}$, $VEGF_{189}$, VEGF2, and VEGF-C. In addition, claims 13-16 and 24 have been cancelled in view of the instant amendments to the claims. New claims 26 and 27 are supported in the specification, for example, on page 3, lines 5-7.

These amendments add no new matter to the application. For the convenience of the Examiner, a marked-up illustration of the claims as amended is attached hereto, as is the text of all claims pending upon entry of the amendments set forth herein.

**Discussion of Enablement Rejection - 35 U.S.C. § 112, first paragraph**

The Office Action rejects claims 1-3, 6-12, 17-23, and 25 under 35 U.S.C. § 112, first paragraph, as allegedly non-enabled. Notwithstanding the rejection, the Office Action indicates that the specification is enabling for (i) the administration of a vector comprising a nucleic acid encoding a vascular endothelial growth factor, wherein the nucleic acid is operably linked to a promoter and (ii) the administration of a vector comprising a nucleic acid encoding a vascular endothelial growth factor and a nucleic acid encoding a second osteotropic protein, to a bone, or within tissue immediately surrounding the bone, wherein the nucleic acids are operably linked to a promoter and whereby bone density or formation is enhanced.

To advance prosecution, the claims are amended hereby to recite that the first nucleic acid of the inventive method encodes a vascular endothelial growth factor. Similarly, the claims are amended hereby to recite that the first nucleic acid of the inventive viral vector encodes a vascular endothelial growth factor. Moreover, the claims are hereby amended to recite that the inventive bone graft comprises at least one first cell having at least one first exogenous nucleic acid encoding a vascular endothelial growth factor. In view of the amendments to the claims, the rejection under 35 U.S.C. § 112, first paragraph, is moot.

**Discussion of Obviousness Rejection - 35 U.S.C. § 103(a)**

The Office Action rejects claims 19-21 as obvious in light of Bonadio. As discussed above, to advance prosecution, claim 19 has been amended to recite that the first nucleic acid encodes a vascular endothelial growth factor. Bonadio does not disclose or suggest a viral vector that has a first nucleic acid encoding a vascular endothelial growth factor and a second nucleic acid encoding an osteogenic protein. As such, Bonadio does not disclose the elements of claims 19-21, nor does it suggest the elements of those claims. Accordingly, Bonadio does not render claims 19-21 obvious, and the rejection under Section 103 should be withdrawn.

**Additional Comments**

Applicants acknowledge, with appreciation, the indication that claims 4, 5, 13-16, and 24 would be allowable if rewritten to include all of the limitations of the base claim and any intervening claims. In view of the instant amendments to the claims, claims 13-16 and 24 have been cancelled. Moreover, Applicants believe that it is unnecessary to rewrite

claims 4 and 5 in view of the instant amendments to claim 1 (from which claims 4 and 5 depend).

**Conclusion**

The application is considered in good and proper form for allowance, and the Examiner is respectfully requested to pass this application to issue. If, in the opinion of the Examiner, a telephone conference would expedite the prosecution of the subject application, the Examiner is invited to call the undersigned attorney.

Respectfully submitted,

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Date: August 5, 2002

M:Clients/Cornell/Amd/205965am3

**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

In re Application of:

Crystal et al.

Application No. 09/629,074

Art Unit: 1632

Examiner: Anne-Marie Baker

Filed: July 31, 2000

For: METHOD OF ENHANCING BONE DENSITY

**ILLUSTRATION OF AMENDMENTS FILED ON AUGUST 5, 2002**

**Amendment to the specification at page 2, line 34, through page 3, line 17:**

The inventive method involves administering a nucleic acid (i.e., a first nucleic acid) encoding an angiogenic protein to a cell (i.e., a first cell) within the region of the bone. An angiogenic protein is any protein that potentiates or enhances neovascularization, many of which are known in the art. While any such factor can be employed in the context of the inventive method, because VEGF proteins are not known to induce the growth of tissues not involved in the production of new vasculature, a preferred angiogenic protein is a VEGF protein (e.g., $VEGF_A$, $VEGF_B$, $VEGF_C$, [~~$FEGF_D$~~] $\underline{VEGF_D}$, $VEGF_E$), and more preferably $VEGF_{121}$, $VEGF_{A138}$, $VEGF_{145}$, $VEGF_{A162}$, $VEGF_{165}$, $VEGF_{182}$, $VEGF_{189}$, or a derivative thereof, (see, e.g., U.S. Patents 5,332,671 (Ferrara *et al.*), 5,240,848 (Keck *et al.*); and 5,219,739 (Tischer *et al.*)). Most preferably, because of their higher biological activity, the angiogenic protein is $VEGF_{121}$ or $VEGF_{165}$, particularly $VEGF_{121}$. Inasmuch as $VEGF_{121}$ typically binds heparin with lesser affinity than does $VEGF_{165}$, $VEGF_{121}$ is particularly preferred for use in the inventive method. While VEGF proteins are preferable for use in the inventive method, other angiogenic proteins include connective tissue growth factor (CTGF), VEGF2, VEGF-C, fibroblast growth factors (FGFs) (e.g., aFGF, bFGF, and FGF-4), angiopoiteins, angiopoetin homologous proteins, angiogenin, angiogenin-2, and P1GF (see, e.g., U.S. Patents 5,194,596, 5,219,739, 5,338,840, 5,532,343, 5,169,764, 5,650,490, 5,643,755, 5,879,672, 5,851,797, 5,843,775, and 5,821,124; International Patent Application WO 95/24473; European Patent Documents 476 983, 506 477, and 550 296; Japanese Patent

Documents 1038100, 2117698, 2279698, and 3178996; and J. Folkman *et al.*, *A Family of Angiogenic Proteins*, *Nature, 329,* 671 (1987)).

**Amendments to the claims:**

1. (Thrice Amended) A method for enhancing bone density or formation, the method comprising administering to at least one first cell associated with a region of a bone at least one first nucleic acid encoding [~~at least one angiogenic protein~~] a vascular endothelial growth factor, such that the first nucleic acid is expressed in the cell to produce the [~~angiogenic protein~~] vascular endothelial growth factor, whereby bone density or formation is enhanced within the region[~~; wherein the angiogenic protein is a vascular endothelial growth factor (VEGF), a connective tissue growth factor (CTGF), VEGF2, VEGF-C, an angiopoitein, an angiogenin, an angiogenin-2, or P1GF~~], wherein the first cell is within the bone or within a tissue immediately surrounding the bone.

4. (Twice Amended) The method of claim 1, wherein the [~~angiogenic protein~~] vascular endothelial growth factor is $VEGF_{121}$ or $VEGF_{165}$.

5. (Twice Amended) The method of claim 1, wherein the [~~angiogenic protein~~] vascular endothelial growth factor is selected from the group consisting of [~~$VEGF_{121}$~~], $VEGFA_{138}$, $VEGFA_{162}$, [~~$VEGF_{165}$~~], $VEGF_{182}$, [~~and~~] $VEGF_{189}$, VEGF2, and VEGF-C.

13. (Cancelled)

14. (Cancelled)

15. (Cancelled)

16. (Cancelled)

19. (Amended) A viral vector comprising at least one first nucleic acid encoding [~~at least one angiogenic protein~~] a vascular endothelial growth factor and at least one second nucleic acid encoding at least one osteogenic protein.

22. (Thrice Amended) A bone graft comprising at least one first cell having at least one first exogenous nucleic acid encoding [at least one angiogenic protein] a vascular endothelial cell growth factor and at least one second cell having at least one second nucleic acid encoding at least one osteogenic protein[~~; wherein the angiogenic protein is a vascular endothelial growth factor (VEGF), a connective tissue growth factor (CTGF), VEGF2, VEGF-C, an angiopoitein, an angiogenin, an angiogenin-2, or P1GF~~].

24. (Cancelled)

26. (New) The viral vector of claim 19, wherein the vascular endothelial growth factor is $VEGF_{121}$ or $VEGF_{165}$.

27. (New) The bone graft of claim 22, wherein the vascular endothelial growth factor is $VEGF_{121}$ or $VEGF_{165}$.

**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

In re Application of:

Crystal et al.

Art Unit: 1632

Application No. 09/629,074

Examiner: Anne-Marie Baker

Filed: July 31, 2000

For: METHOD OF ENHANCING BONE DENSITY

**CLAIMS PENDING UPON ENTRY OF THE AMENDMENTS OF AUGUST 5, 2002**

1. A method for enhancing bone density or formation, the method comprising administering to at least one first cell associated with a region of a bone at least one first nucleic acid encoding a vascular endothelial growth factor, such that the first nucleic acid is expressed in the cell to produce the vascular endothelial growth factor, whereby bone density or formation is enhanced within the region, wherein the first cell is within the bone or within a tissue immediately surrounding the bone.

2. The method of claim 1, wherein at least one of the nucleic acids is exposed to at least one cell in vivo in the region of the bone.

3. The method of claim 1, wherein at least one of the nucleic acids is exposed to at least one cell ex vivo, which is then delivered in vivo to the region of the bone.

4. The method of claim 1, wherein the vascular endothelial growth factor is $VEGF_{121}$ or $VEGF_{165}$.

5. The method of claim 1, wherein the vascular endothelial growth factor is selected from the group consisting of $VEGFA_{138}$, $VEGFA_{162}$, $VEGF_{182}$, $VEGF_{189}$, VEGF2, and VEGF-C.

6. The method of claim 1, further comprising administering to at least one second cell associated with the region at least one second nucleic acid encoding at least one osteogenic protein, such that the second nucleic acid is expressed in the cell to produce the osteogenic protein, wherein the second cell is within the bone or within a tissue immediately surrounding the bone.

7. The method of claim 6, wherein the osteogenic protein is selected from the group consisting of a bone morphogenic protein (BMP), a transforming growth factor (TGF), a latent TGF binding protein (LTBP), latent membrane protein-1 (LMP-1), a heparin-binding neurotrophic factor (HBNF), growth and differentiation factor-5 (GDF-5), a parathyroid hormone (PTH), a fibroblast growth factor (FGF), an epidermal growth factor (EGF), a platelet-derived growth factor (PDGF), an insulin-like growth factor, a

growth factor receptor, a cytokine, a chemotactic factor, a LIM mineralization protein (LMP), a leukemia inhibitory factor (LIF), a hedgehog protein, and midkine (MK).

8. The method of claim 6, wherein the osteogenic protein is selected from the group consisting of BMP-2, BMP-3, BMP-4, BMP-5, BMP-6, BMP-7 and BMP-8.

9. The method of claim 6, wherein the osteogenic protein is TGF-b1.

10. The method of claim 6, wherein the osteogenic protein is BMP-2.

11. The method of claim 6, wherein the osteogenic protein is MK.

12. The method of claim 6, wherein the osteogenic protein is HBNF.

17. The method of claim 6, wherein the first cell and the second cell are the same cell.

18. The method of claim 6, wherein the first nucleic acid and the second nucleic acid are the same nucleic acid.

19. A viral vector comprising at least one first nucleic acid encoding a vascular endothelial growth factor and at least one second nucleic acid encoding at least one osteogenic protein.

20. The viral vector of claim 19, which is an adenoviral vector.

21. The viral vector 19, which is deficient in at least one essential gene function.

22. A bone graft comprising at least one first cell having at least one first exogenous nucleic acid encoding a vascular endothelial growth factor and at least one second cell having at least one second nucleic acid encoding at least one osteogenic protein.

23. The bone graft of claim 22, wherein the osteogenic protein is selected from the group consisting of a bone morphogenic protein (BMP), a transforming growth factor (TGF), a latent TGF binding protein (LTBP), latent membrane protein-1 (LMP-1), a heparin-binding neurotrophic factor (HBNF), growth and differentiation factor-5 (GDF-5), a parathyroid hormone (PTH), a fibroblast growth factor (FGF), an epidermal growth factor (EGF), a platelet-derived growth factor (PDGF), an insulin-like growth factor (IGF), a growth factor receptor, a cytokine, a chemotactic factor, a LIM mineralization protein (LMP), a leukemia inhibitory factor (LIF), a hedgehog protein, and midkine (MK).

25. The bone graft of claim 22, which is an allograft.

26. The viral vector of claim 19, wherein the vascular endothelial growth factor is $VEGF_{121}$ or $VEGF_{165}$.

27. The bone graft of claim 22, wherein the vascular endothelial growth factor is $VEGF_{121}$ or $VEGF_{165}$.